REMARKS

Claims 25-38 are pending in this application. By this Amendment, claims 25-38 are added and claims 1-24 are canceled. Support for the amendments to the claims may be found, for example, in the claims and specification as originally filed. No new matter is added.

In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

Applicants thank Examiner Aulakh for the courtesies extended their representative at the July 25, 2008, personal interview. Applicants' separate record of the substance of the interview is incorporated into the following remarks.

I. Rejections under 35 U.S.C. §112

A. 35 U.S.C. §112, First Paragraph

The Office Action rejects claims 1-24 under the enablement requirement of 35 U.S.C. §112, first paragraph. By this Amendment, claims 1-24 are canceled, rendering their rejection moot. New claims 25-38 do not recite "or solvates thereof" and, therefore, should overcome the enablement rejection as applied to claims 1-8.

The Office Action asserts that there is no teaching or guidance present in the specification or prior art that hyperactivity of T-type calcium channel is implicated in the etiology of hypercardia, heart failure, cardiomyopathy, arterial fibrillation, arrhythmia, arterial sclerosis, nephritis, nephropathy, renal disorder, renal insufficiency, edema, inflammation, hyperaldosteronism, neurogenic pain and epilepsy. Applicants respectfully disagree. The specification cites numerous references in support of its disclosure of the potentially therapeutic effects of the presently claimed compounds in regard to the specified disease states to which claims 33-35 are drawn. *See* specification, paragraph [0005].

The Office Action asserts that there is no teaching in the prior art that structurally closely related compounds having antagonistic activity at T-type calcium channels are well

known to have therapeutic utility in treating hypercardia, heart failure, cardiomyopathy arterial fibrillation, arrhythmia, arterial sclerosis, nephritis, nephropathy, renal disorder, renal insufficiency, edema, inflammation, hyperaldosteronism, neurogenic pain and epilepsy. Applicants respectfully submit herewith references detailing clinical investigations of the therapeutic uses of T-type calcium channel blockers in varied disease states. While the specific T-type calcium channel blockers utilized in the reference studies do not appear to be closely structurally related, they, like the compound of the presently claimed invention, successfully exhibit antagonist activity at T-type calcium channels. In the reference studies submitted herewith, several structurally unrelated T-type calcium channel blockers were shown to be similarly therapeutically effective.

Accordingly, new claims 25-38 satisfy the requirements of 35 U.S.C. §112, first paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

B. 35 U.S.C. §112, Second Paragraph

The Office Action rejects claims 9-24 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. By this Amendment, claims 9-24 are canceled, rendering their rejection moot.

Reconsideration and withdrawal of the rejection are respectfully requested.

II. Rejection under 35 U.S.C. §103

The Office Action rejects claims 1-24 under 35 U.S.C. §103(a) as being unpatentable over Masumiya et al., European Journal of Pharmacology, 335 (1997) 15-21 ("Masumiya"), in view of U.S. Patent No. 4,535,073 to Kimura et al. ("Kimura"). By this Amendment, claims 1-24 are canceled, rendering their rejection moot.

Reconsideration and withdrawal of the rejection are respectfully requested.

III. New Claims

By this Amendment, claims 25-38 are added. Claims 25-38 are based upon claims 1-6, 18, 22, and 23 as originally filed.

The optically-active 1,4-dihydropyridine compounds of claims 25-32 are not taught by Masumiya and Kimura. Specifically, Masumiya provides test results for the use of recemic efonidipine, but does not specifically disclose or report the R-efonidipine. Kimura discloses that dihydropyridine compounds have an asymmetric carbon atom, optically active compounds are present, and thus the optically active compounds can be obtained by forming salts with an optically active acid or base. See col. 5, lines 24-30. However, the presence of optically active compounds that show selective blocking action against T-type calcium channel according to the present claims could not have been expected from a combination of Masumiya and Kimura, and thus Masumiya and Kimura would not have rendered obvious the present claims.

Claims 33-38 are method of treatment claims which are drawn to treating renal disorder, hyperaldosteronism and neurogenic pain, respectively.

Additionally, submitted herewith are three references which document the therapeutic utility of T-type calcium channel blockers similar to the presently claimed invention. Sugano et al. examined the protective role of the stereo selective T-type calcium channel blocker R(–)-efonidipine in spontaneously hypertensive rats (SHR). They demonstrated that efonidipine improves proteinuria and glomerular hypertrophy and reduces systolic blood pressure in subtotally nephrectomized SHR – clearly indicating that specific blockade of T-type calcium channels offers renal protective action. Sugano et al., *Kidney International* (2008) 73, pp. 826-834.

Baylis et al. investigated whether combined T- and L-type CCBs (calcium channel blockers) provided superior protection against chronic renal disease versus traditional L-type

voltage-gated CCBs. Baylis et al. found that the combined T- and L-type CCB mibefradil is renoprotective in the rapidly progressing model of kidney disease produced by DOCA-salt and uninephrectomy. Baylis et al., *American Journal of Kidney Diseases*, Vol. 38, No. 6 (December), 2001: pp. 1292-1297.

Imagawa et al. found efonidipine to exert an inhibitory effect on aldesterone synthesis and secretion in a human adrenocortical cell line. Imagawa et al., *Cardiovasc Pharmacol.*, Volume 47, Number 1, January 2006. In studies investigating the effect of T-type calcium channel blockers on neuropathic pain, Dogrul et al. found that administration of systemic mibefradil or ethosuximide (a T-type CCB) produced a dos-dependent blockade of both tactile and thermal hypersensitivities in nerve injured rats. Dogrul et al., *Pain* 105 (2003) pp. 159-168.

Therefore, the references discussed above demonstrate that T-type calcium channel blockers have therapeutically effective for renal disorder, hyperaldosteronism and neurogenic pain. The current specification establishes that the claimed compounds are T-type calcium channel blockers. *See*, e.g., specification at page 20 (table). As such, Applicants respectfully submit that the claimed compounds would also be therapeutically effective for renal disorder, hyperaldosteronism and neurogenic pain.

IV. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

James A. Oliff
Registration No. 27,075

Joel S. Armstrong
Registration No. 36,430

JAO:JRB:JSA

Date: July 29, 2008

Attachments:

Sugano et al., *Kidney International* (2008) 73, pp. 826-834
Baylis et al., *American Journal of Kidney Diseases*, Vol. 38, No. 6 (December, 2001): 1292-1297
Dogrul et al., *Pain* 105 (2003) pp. 159-168

OLIFF & BERRIDGE, PLC
P.O. Box 320850
Alexandria, Virginia 22320-4850
Telephone: (703) 836-6400

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